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Management of Pharyngeal Gonorrhea Is Crucial To Prevent the Emergence and Spread of Antibiotic-Resistant *Neisseria gonorrhoeae*

We read with great interest the paper recently published by Unemo et al. that reported a second strain (F89) of *Neisseria gonorrhoeae* with a high level of ceftriaxone resistance, for which the ceftriaxone MIC was 1 μg/ml, that was isolated in France in 2010 (10). The first high-level ceftriaxone-resistant strain (H041), for which the ceftriaxone MIC was 2 μg/ml, was isolated in Japan in 2009 (7). The emergence of such strains would be a matter of great concern for treatment of gonorrhea.

Cephalosporins are the last antibiotics remaining that are the most reliable and available for treatment of gonorrhea. However, clinical strains of *N. gonorrhoeae* with decreased susceptibilities to oral cephalosporins, for which cefixime MICs ranged from 0.25 to 1 μg/ml, have emerged since the early 2000s (4). In such strains, a mosaic-like structure of the *penA* gene, encoding penicillin-binding protein (PBP) 2, was found (1). The mosaic PBP 2 that we named pattern X was significantly associated with decreased susceptibilities to oral cephalosporins (3). The mosaic structure of PBP 2 is composed of fragments analogous to those from PBP 2 in *Neisseria cinerea* and *Neisseria perflava*, which are commensal in the nasopharynx (3). *N. gonorrhoeae* would have undertaken interspecies exchanges of the *penA* gene with the commensal *Neisseria* and acquired a mosaic *penA* gene in the pharynx. For gonococcal urethritis caused by strains with mosaic PBP 2, treatment failures with cefixime regimens have been reported (12). For strains with mosaic PBP 2, however, ceftriaxone MICs ranged from 0.015 to 0.25 μg/ml and were still within the susceptible range for ceftriaxone (3, 6). The high-level ceftriaxone-resistant strains (H041 and F89) had novel mosaic patterns of PBP 2 in which only a few amino acids changed compared with those associated with decreased susceptibilities to oral cephalosporins (7, 10). They would have evolved out of strains harboring the mosaic PBP 2 associated with decreased susceptibilities to oral cephalosporins.

In 2010, ceftriaxone treatment failure of pharyngeal gonorrhea was observed in Sweden (9). The causative strains were susceptible to ceftriaxone but had the mosaic PBP 2 associated with decreased susceptibilities to oral cephalosporins. The difficulties in treatment of pharyngeal gonorrhea compared with the treatment of urogenital infections could be due to lower concentrations of antibiotics in the pharyngeal mucosa. The high-level ceftriaxone-resistant strain H041 was isolated from the pharynx of a female commercial sex worker (7). The other strain, F89, was isolated from the urethra of a man who had sex with men (MSM) (10). This strain might have been derived from the pharynx, because gonococcal urethritis in MSM could be transmitted by fellatio as well as insertive anal intercourse (2). Selection of ceftriaxone resistance could occur more frequently in the pharynx than at the urogenital and anorectal sites. To make matters worse, selected strains could persist in the pharynx without further treatment because most cases of pharyngeal gonorrhea are asymptomatic. In this context, more attention should be paid to the diagnosis and treatment of pharyngeal gonorrhea. The detection of *N. gonorrhoeae* from the pharynx and the determination of its antimicrobial resistance would be crucial. The sensitivity of nucleic acid amplification tests (NAATs) for the detection of *N. gonorrhoeae* in nongenital anatomic sites is superior to that of culture (8), but NAATs cannot provide antimicrobial susceptibility. Although the development of molecular assays that do not involve culturing of *N. gonorrhoeae* and testing of *in vitro* antimicrobial susceptibility is needed to assess the antimicrobial resistance of *N. gonorrhoeae* (5), NAATs would be more useful in clinical settings. For treatment of pharyngeal gonorrhea, dual treatment with ceftriaxone and azithromycin is currently recommended (11), but higher doses and/or multiple doses of ceftriaxone might be required to prevent the emergence of ceftriaxone resistance. After treatment of pharyngeal gonorrhea, test-of-cure might be needed in patients with no pharyngeal symptoms. A new management algorithm for pharyngeal gonorrhea should be established immediately.

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